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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 11/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/825,566	LAIRD ET AL.	
	Examiner	Art Unit	
	Jehanne S Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *21-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/2001*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group XII, corresponding to MYOD1 gene, claims 1-20 in the reply filed on 8/9/2004 is acknowledged. The traversal is on the ground(s) that the kits have limited diagnostic utility for determining methylation status of CpG dinucleotides of specific amplicons corresponding to the oligomer sequences of Groups I-XX. This is not found persuasive because the claims as presently written are broader than sequences which have the diagnostic utility asserted in the response. Each of the 4 kit claims either recites sequences to MYOD1 generically, or stipulates that the kits contain sequences which comprise "at least about 12 to 15" nucleotides of the listed SEQ ID NOS:. Since the use for a kit carries no patentably weight, and the additional kit components recite no more than standard PCR reagents, such as buffer or a polymerase, the kits actually read on compositions that contain sequences that could function to hybridize to a particular sequence of MYOD1, for example, but also to another nucleic acid sequence and not be used in detecting methylation of MYOD1. This is true for claim 24 as well, drawn to a kit comprising an array which only minimally must comprise fragments of the claimed SEQ ID NOS:, thus requiring a search of the array art for sequences which are broader structurally than sequences from only within MYOD1. The search for prior art and for 112/first paragraph issues for a kit is not constrained by the use for a kit and is therefor much broader and not coextensive with the claims drawn to methods. Additionally, none of the kit claims are constrained to the same structural requirements for the claimed SEQ ID NOS as the method claims, further proof that the search for the claimed compositions are broader than those of the method. For these reasons, the nucleic acids in the kit claims are not

constrained to be methylated portions of MYOD1 and do encompass sequences which can be used to encode peptides, or be used as aptamers, for example, which are not required for the methods of claims 1-20. Art for the purposes of 112/first paragraph, 102, and 103 rejections for the method claims does not represent the search for the full scope encompassed by the kit claims nor even the majority of the search required for the kits. Also, a search for MYOD1 generally, would not necessarily provide art relevant for cancer diagnosis, which is required for the search for the method claims. As specifically outlined above, the search for method claims is not coextensive with the search for the kits and represents a search burden as the search for each invention is not coextensive. As such, the claims directed to methods and products represent patentably distinct inventions which would pose a burden on the office in searching both.

The requirement is still deemed proper and is therefore made FINAL.

2. An action on the merits of claims 1-20, directed to MYOD1 follows.

Priority

3. Claims 1-10 and 15-20 are not awarded benefit of the priority date of the provisional application, 60/193,839, from which the instant specification claims priority, because the claims are broader than the invention disclosed in the '839 application. The '839 application only taught methods of diagnosing gastrointestinal cancers, whereas the instantly examined claims are drawn to diagnosing any cancer. Claim 1-10 and 15-20 are therefor awarded the priority date of the instantly filed specification: 4/2/2001, while claims 11-14 are awarded benefit of the date of filing of the provisional application: 3/31/2000.

Specification

4. The amendment filed 8/9/2004, to the sequence listing, is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The sequence listing has been amended to include the sequences of SEQ ID NOS: 66-76. Upon thorough review of the specification, however, it has been determined that the specification does not provide support for the sequences of SEQ ID NOS 66-76 for the reasons which follow.

SEQ ID NO: 66 represents the MYOD1 genomic sequence of Genbank Accession number given in table II. However, sequences in Genbank can be changed. The objection with regard to SEQ ID NO: 66 could be overcome with a declaration stating that the sequence of SEQ ID NO: 66 is the sequence of the Genbank Accession number that was used at the time the invention was made, before the filing of the instant application or that of the provisional application.

SEQ ID NO: 67 corresponds to "CpG island portion of SEQ ID NO: 66". The response asserts that it finds support by the definition of CpG islands given at pages 7 and 8 of the specification as originally filed. The specification was thoroughly reviewed, however it was not found to provide support for the specific molecule of SEQ ID NO: 67. While the specification generally teaches what CpG islands are, and also states that they 1) have a frequency of CpG dinucleotides corresponding to an 'observed/expected' ratio >.6 and 2) have a GC content >.5, such teaching, it is clear from the definitions set forth at page 7 that these values are dependent on the length of the DNA fragment. The specification does not make clear how it would be

determined what the cutoff points (ie: how long the fragments are) for the molecule were, how big the molecule was etc. For example, if the sequence of SEQ ID NO: 67 were truncated by one nucleotide on either end, would it still provide acceptable ratio and GC content? No indication is given in the specification, of any formula that could be used such that the only result for a CpG island 'portion' would be that of SEQ ID NO: 67. Accordingly, one of ordinary skill in the art reading the contents of the specification would not be immediately aware of the specific sequence of SEQ ID NO: 67 given the disclosure in the specification at the time it was originally filed. Further, it does not appear that given the formulas in the specification, the only molecule that would result from the given accession number would be the specific molecule of SEQ ID NO: 67.

The response asserts further that SEQ ID NOS: 68-76 correspond to fully upmethylated, or downmethylated sense and antisense sequences corresponding to either the genomic 'CpG island portion' of SEQ ID NO: 67 (SEQ ID NOS 68-71) or the genomic treated (SEQ ID NO: 72) sequence of MYOD1 defined by the forward and reverse primers of SEQ ID NOS 7 and 8 (SEQ ID NOS 73-76). The response asserts that such sequences find support at page 20, line 12 through page 21, line 35 of the specification. The specification, however, only generally discusses bisulfite treatment, the use of primers in such analysis, and the case of either fully methylated or fully unmethylated *primers*. It is known in the art, and acknowledged by the specification, that genomic CpG islands are not necessarily fully up or down methylated, in diseases, or in general. The specification provides no support for fully upmethylated or downmethylated genomic MYOD1 sequences, and therefore does not provide support for the sequences of SEQ ID NOS: 68-71, or SEQ ID NOS: 73-76. With regard to SEQ ID NO: 72, the

response asserts that it is "genomic MYOD1 sequence corresponding to treated DNA amplicon" defined by primers SEQ ID NO: 7 and 8. It is unclear how this sequence is different from SEQ ID NOS: 66, 67, or 73. A review of the specification, however, indicates that the specification provides no support for the specific sequence of SEQ ID NO: 72 or how this sequence is "treated".

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing breast cancer in a breast tissue sample by detecting hypermethylation of CpG islands in the MYOD1 gene, esophageal carcinoma in an esophageal tissue sample by detecting hypermethylation of CpG islands in the MYOD1 gene, colorectal carcinoma in a colorectal tissue sample by detecting hypermethylation of CpG islands in the MYOD1 gene, or Embryonal rhabdomyosarcoma in a muscle tissue by detecting partial methylation of CpG islands in the MYOD1 gene or Alveolar rhabdomyosarcoma in muscle tissue by detecting hypomethylation of CpG islands in the MYOD1, does not reasonably provide enablement for diagnosis or prognosis of any type of cancer or gastrointestinal cancer in any tissue sample by detecting any type of methylation such as hypermethylation, hypomethylation or normal methylation in the MYOD1 gene. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are broadly drawn to diagnosis or prognosis of any type of cancer or gastrointestinal cancer in any tissue sample by detecting any type of methylation such as hypermethylation, hypomethylation or normal methylation in the MYOD1 gene. The claims encompass a method of making any diagnostic or prognostic prediction or determination of any type of cancer or cancer related condition based on any methylation status of the MYOD1 gene in any tissue sample.

The amount of direction or guidance and Presence and absence of working examples:

The specification teaches that CpG islands in the promoter region of the MYOD1 gene was hypermethylated in intestinal metaplasia tissue as compared to normal esophageal tissue (see page 36, lines 4-6). The specification teaches that increases in MYOD1 methylation were found

in esophageal adenocarcinoma, Barrett's esophagus, and dysplasia (see Fig. 1). The specification further teaches that MYOD1 hypermethylation was correlated with increases in tumor stage (see Fig. 4, page 38). The specification is silent, however, to any association between methylation of MYOD1 and diagnosis or prognosis, even at least in part, of any cancer or any gastrointestinal carcinoma, or any cancer related condition.

The state of the prior art and the predictability or unpredictability of the art:

While the specification is silent with regard to breast and colon cancers as well as rhabdomyosarcomas, the prior art is enabling for methods of cancer diagnosis or prognosis with regard to breast (see Hahnel et al, Anticancer Research, vol. 16, pages 2111-2116; 1996), colorectal (see Iacopetta et al; Int. J. of Cancer, vol. 17, pages 429-432, 1997), and rhabdomyosarcoma (See Chen et al; American Journal of Pathology, vol. 152, pages 1071-1079; 1998, or Chen: US Patent 6180,344), wherein hypermethylation in CpG islands in the MYOD1 gene from breast or colorectal tissue samples is indicative of higher tumor grade with regard to breast cancer or is indicative of colorectal cancer with regard to colon cancer, or wherein partial methylation in CpG islands in the MYOD1 gene in muscle tissue is indicative of embryonal rhabdomyosarcoma or wherein hypomethylation in CpG islands in the MYOD1 gene in muscle tissue is indicative of Alveolar rhabdomyosarcoma. However, no universal correlation is taught in the prior art with regard to the ability to diagnose or prognose any cancer, even only in part based on the methylation status of CpG islands in the MYOD1 gene. For example, Taylor et al (Taylor et al; Leukemia, vol. 15, pages 583-589, 2001) teach that while 93% of non Hodgekin lymphoma or lymphoid leukemia had increased Myf-3 (MYOD1) methylation, there was not alteration in 92% of patients with Hodgekin lymphoma or in normal tissue (see abstract).

Further, Yu et al (Yu et al; Cell Research, vol. 13, pages 319-333; 2003) teach that MYOD1 methylation changes were similar in both normal liver tissue as well as HCC tissue samples (see page 324, col. 2). Additionally, it is noted that the claims are drawn to specifically detecting gastrointestinal cancer based on MYOD1 methylation. While the specification teaches alterations in MYOD1 CpG island methylation for esophageal carcinoma, the specification is silent with regard to gastrointestinal cancer and the art does not provide for a universal correlation that CpG island methylation changes in one gene which is associated with Esophageal carcinoma is also associated with gastrointestinal cancer. Kawakami et al (Kawakami et al; Journal of the National Cancer Institute, vol. 92, pages 1805-1811, 2000) teach that while hypermethylation of CpG islands in the APC gene promoter is characteristic for primary esophageal cancer and Barrett's Esophageal tissue, it was also found in normal gastric epithelium (see pages 1807-1808, col. 1). The teachings in the art therefore demonstrate that no predictable correlation can be made with regard to the type of methylation alteration (ie: hypermethylation vs hypomethylation) in any given gene which possesses CpG island methylation patterns, nor that methylation alterations in any given gene will be predictably correlative of diagnosis or prognosis for any given cancer.

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

Based on the limited guidance in the specification, and the unpredictability taught in the art, it would require undue experimentation for one of skill in the art to practice the invention as broadly as it is claimed. The skilled artisan would have to screen a large number of different tissue samples in patients with many different types of cancer to determine whether normal methylation, hypermethylation, or hypomethylation was diagnostic or prognostic for any type of cancer based on analysis of any specific type or general tissue. Based on the unpredictability in the art and the lack of guidance in the specification with regard to diagnosis of any type of cancer or cancer related condition other than for esophageal cancer and Barrett's esophageal as outlined in the specification, it is clear that such experimentation would require an extremely large amount of unpredictable trial and error analysis. It also is noted that the claims do not set forth any specific methylation alteration in the MYOD1 gene from any tissue sample. The claims merely set forth an invitation to experiment as they leave it up to the skilled artisan to determine if an increase or decrease in methylation of MYOD1 compared to methylation in a control subject is indicative of any specific cancer. While hypermethylation of CpG islands of promoters of some genes involved in cancer have been associated with esophageal cancer, the specification has not set forth any predictable correlation that hypomethylation or hypermethylation of MYOD1 is indicative of any type of cancer. Additionally, the claims encompass methods wherein the mere detection of methylation in MYOD1 from any tissue sample will be indicative of or prognostic for any cancer or cancer related condition. However, the specification has not established that methylation status as compared to normal subjects, of the promoter of any nucleic acid from a sample taken from liver, for example, will be indicative

of esophageal cancer, as opposed to a cancer of the liver. The specification provides no evidence of a predictable correlation between diagnosis of esophageal cancer or Barrett's esophageal and hypermethylation or hypomethylation of MYOD1 taken from a liver sample. The art demonstrates that hypermethylation of the promoter region of a number of different genes has been correlated to a number of different cancers. For example, GSTP1 promoter hypermethylation has been associated with prostate, renal, and breast cancer (see Esteller et al; Cancer Research, vol. 58, pp 4515-4518; 1998). However, Esteller does not teach, and the skilled artisan would not conclude based on the teachings of Esteller, that detection of GSTP1 hypermethylation in a prostatic sample would be indicative of renal cancer. Based on the lack of guidance in the specification and the unpredictability taught in the art with regard to an association between methylation status of any nucleic acid from any specimen and esophageal cancer, undue experimentation would be required of the skilled artisan to practice the invention as broadly as it is claimed. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of any working examples other than for esophageal tissue and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 1-3, 5-8, 10, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Iacopetta (Iacopetta et al; Int. J. of Cancer, vol. 17, pages 429-432, 1997).

With regard to claims 1 and 6, Iacopetta teaches that regional hypermethylation of the Myf-3 (MYOD1) gene is an early and widespread event in colorectal neoplasia (see page 432, last para). The method of Iacopetta involves obtaining tissue from a test tissue to be diagnosed (see page 429, col. 2, 2nd full para; colorectal tissue), performing a methylation assay using restriction enzymes and nucleic acid probes (see page 429-430 bridging para; probe to 3' downstream region of Myf-3) to determine the methylation state of genomic CpG sequence for Myf-3. Iacopetta teaches that hypermethylation of the Myf-3 gene is strongly associated with the development of benign and malignant colorectal tumors, therefore Iacopetta teaches "making a diagnostic or prognostic prediction of the cancer based at least in part on the methylation state of the genomic CpG sequences (see page 431, col. 1, first sentence of "Discussion").

With regard to claims 2, 5, 7, and 10: the CpG sequences analyzed by Iacopetta inherently 'correspond to CpG islands' which are 'associated' with sequences defined by SEQ ID NOS 7-9. It is noted that this recitation has been broadly interpreted to encompass the gene

which can be analyzed by the recited SEQ ID NOS in the claim. The claims do not require analysis with the specifically recited SEQ ID NOS:.

With regard to claims 3 and 8, the MYOD1 gene analyzed by Iacopetta is inherently "defined by the oligonucleotide primers and probes" of SEQ IDNOS 7-9. It is noted that this recitation has been broadly interpreted to encompass the gene which is can be analyzed by the recited SEQ ID NOS in the claim. The claims do not require analysis with the specifically recited SEQ ID NOS:.

With regard to claim 20, Iacopetta teaches detecting extensive hypermethylation in adenomas and malignant colorectal tumors (see page 431, para bridging cols 1 and 2).

9. Claims 1-3, 5-8, 10, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Hahnel (Hahnel et al; Anticancer Research, vol. 16, pages 2111-2116; 1996).

With regard to claims 1 and 6, Hahnel teaches a method which involves obtaining tissue from a test tissue to be diagnosed (see page 2111, col. 2, first full para; breast tissue), performing a methylation assay using restriction enzymes and nucleic acid probes (see page 2112 bridging para cols 1-2; probe to 3' downstream region of Myf-3) to determine the methylation state of genomic CpG sequence for Myf-3. Hahnel teaches that there was a statistically significant differenced in the hypermethylation (instant claim 20) in grade 3 carcinomas (see page 2112, 2nd col. Last para) and further teaches that hypermethylation of the Myf-3 gene was much more common in poorly differentiated (grade 3) breast carcinomas than in well differentiated tumors (grade 1 or 2) (see page 2114, col. 2), therefore Hahnel teaches "making a diagnostic or

prognostic prediction of the cancer based at least in part on the methylation state of the genomic CpG sequences (see page 431, col. 1, first sentence of "Discussion").

With regard to claims 2, 5, 7, and 10: the CpG sequences analyzed by Hahnel inherently 'correspond to CpG islands' which are 'associated' with sequences defined by SEQ ID NOS 7-9. It is noted that this recitation has been broadly interpreted to encompass the gene which can be analyzed by the recited SEQ ID NOS in the claim. The claims do not require analysis with the specifically recited SEQ ID NOS:.

With regard to claims 3 and 8, the MYOD1 gene analyzed by Hahnel is inherently "defined by the oligonucleotide primers and probes" of SEQ IDNOS 7-9. It is noted that this recitation has been broadly interpreted to encompass the gene which is can be analyzed by the recited SEQ ID NOS in the claim. The claims do not require analysis with the specifically recited SEQ ID NOS:.

10. Claims 1-10, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen I (Chen et al; American Journal of Pathology, vol. 152, pages 1071-1079; 1998).

With regard to claims 1 and 6, Chen I teaches that methylation alterations in the upstream region of the MYOD1 gene are predictive of subclassification of Rhabdomyosarcomas (see abstract). The method of Chen I involves obtaining tissue from a test tissue to be diagnosed (see page 1072, col. 2, 2nd full para), performing a methylation assay using restriction enzymes and nucleic acid probes (see page 1072-1073, bridging para) or methylation sensitive PCR (se page 1073, col. 2) to determine the methylation state of genomic CpG sequence for MYOD1; and making a diagnostic or prognostic prediction of the cancer based on the methylation state of the

genomic CpG sequences (see page 1074, last para in col. 2 to page 1075) as Chen I teaches that embryonal rhabdomyosarcomas are characterized by partial methylation of MYOD1 upstream CpG sites and alveolar rhabdomyosarcomas are characterized by hypomethylation of the MYOD1 upstream CpG sites.

With regard to claims 2, 5, 7, and 10: the CpG sequences analyzed by Chen I inherently 'correspond to CpG islands' (it is noted that the sequence analyzed by Chen I is the same accession number disclosed in the instant specification; see page 1074, col. 1, para 1) which are 'associated' with sequences defined by SEQ ID NOS 7-9. It is noted that this recitation has been broadly interpreted to encompass the gene which can be analyzed by the recited SEQ ID NOS in the claim. The claims do not require analysis with the specifically recited SEQ ID NOS:.

With regard to claims 3 and 8, the MYOD1 gene analyzed by Chen I is inherently "defined by the oligonucleotide primers and probes" of SEQ IDNOS 7-9. It is noted that this recitation has been broadly interpreted to encompass the gene which is can be analyzed by the recited SEQ ID NOS in the claim. The claims do not require analysis with the specifically recited SEQ ID NOS:.

With regard to claim 20, Chen I teaches detecting partial methylation and hypomethylation as Chen teaches that embryonal rhabdomyosarcomas are characterized by partial methylation of MYOD1 upstream CpG sites and alveolar rhabdomyosarcomas are characterized by hypomethylation of the MYOD1 upstream CpG sites.

With regard to claims 4 and 9, Chen I teaches detecting methylation alterations in the MYOD1 5' upstream region, which comprises the promoter.

11. Claims 1-10 and 20 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Chen II (Bin Chen; US Patent 6,180,344).

With regard to instant claims 1, 2, 4, 6, 7, 9, and 20 Chen II teaches and claims a method of determining the neoplastic state of tissues by isolated DNA from tissues and performing a methylation sensitive PCR assay on the genomic DNA to determine the methylation state of the CpG island in 5' upstream region comprising the promoter of the MYOD1 gene, wherein partially methylated DNA is indicative of embryonal rhabdomyosarcoma (see abstract, col. 16, lines42-col. 9, line 20; claims 7, 8, and 12 of Chen II). Chen II also teaches that the MYOD1 upstream region is characterized by hypomethylation (see col. 17-18, example 9).

With regard to instant claims 5, and 10: the CpG sequences analyzed by Chen II inherently 'correspond to CpG islands' which are 'associated' with sequences defined by SEQ ID NOS 7-9. It is noted that this recitation has been broadly interpreted to encompass the gene which can be analyzed by the recited SEQ ID NOS in the claim. The claims do not require analysis with the specifically recited SEQ ID NOS:.

With regard to instant claims 3 and 8, the MYOD1 gene analyzed by Chen II is inherently "defined by the oligonucleotide primers and probes" of SEQ IDNOS 7-9. It is noted that this recitation has been broadly interpreted to encompass the gene which is can be analyzed by the recited SEQ ID NOS in the claim. The claims do not require analysis with the specifically recited SEQ ID NOS:.

*Applicant's should note that in overcoming a reference under 35 USC 102(e) which claims the same or an obvious variation (the use of the reference in a 103 rejection below) of the instantly claimed invention, MPEP 706.02(b) part D. states:

When the claims of the reference U.S. patent or U.S. patent application publication and the application are directed to the same invention or are obvious variants, an affidavit or declaration under 37 CFR 1.131 is not an acceptable method of overcoming the rejection.

Further MPEP 715.05 states with regard to the date the patent was published:

When the reference in question is a noncommonly owned U.S. patent or patent application publication claiming the same invention as applicant and its publication date is less than 1 year prior to the presentation of claims to that invention in the application being examined, applicant's remedy, if any, must be by way of 37 CFR 1.608 instead of 37 CFR 1.131.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 15-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen I or Chen II or Iacopetta or Hahnel, each in view of Huang (Huang et al; Human Molecular Genetics, vol. 8, pages 459-470, 1999).

Chen I teaches that methylation alterations in the upstream region of the MYOD1 gene are predictive of subclassification of Rhabdomyosarcomas (see abstract). The method of Chen I involves obtaining tissue from a test tissue to be diagnosed (see page 1072, col. 2, 2nd full para), performing a methylation assay using restriction enzymes and nucleic acid probes (see page 1072-1073, bridging para) or methylation sensitive PCR (se page 1073, col. 2) to determine the methylation state of genomic CpG sequence for MYOD1; and making a diagnostic or prognostic prediction of the cancer based on the methylation state of the genomic CpG sequences (see page 1074, last para in col. 2 to page 1075) as Chen I teaches that embryonal rhabdomyosarcomas are characterized by partial methylation of MYOD1 upstream CpG sites and alveolar rhabdomyosarcomas are characterized by hypomethylation of the MYOD1 upstream CpG sites. With regard to claim 18: the CpG sequences analyzed by Chen I 'correspond to CpG islands' (it is noted that the sequence analyzed by Chen I is the same accession number disclosed in the instant specification; see page 1074, col. 1, para 1) which are 'associated' with sequences defined by SEQ ID NOS 7-9. It is noted that this recitation has been broadly interpreted to encompass the gene which is can be analyzed by the recited SEQ ID NOS in the claim. With regard to claim 19, the MYOD1 gene analyzed by Chen I is "defined by the oligonucleotide primers and probes" of SEQ IDNOS 7-9. It is noted that this recitation has been broadly interpreted to encompass the gene which is can be analyzed by the recited SEQ ID NOS in the claim. The claims do not require analysis with the specifically recited SEQ ID NOS:.

Chen II teaches and claims, with regard to instant claims 1, 2, 4, 6, 7, 9, and 20, a method of determining the neoplastic state of tissues by isolated DNA from tissues and performing a methylation sensitive PCR assay on the genomic DNA to determine the methylation state of the

CpG island in 5' upstream region comprising the promoter of the MYOD1 gene, wherein partially methylated DNA is indicative of embryonal rhabdomyosarcoma (see abstract, col. 16, lines42-col. 9, line 20; claims 7, 8, and 12 of Chen II). Chen II also teaches that the MYOD1 upstream region is characterized by hypomethylation (see col. 17-18, example 9). With regard to claim 18: the CpG sequences analyzed by Chen II 'correspond to CpG islands' which are 'associated' with sequences defined by SEQ ID NOS 7-9. It is noted that this recitation has been broadly interpreted to encompass the gene which is can be analyzed by the recited SEQ ID NOS in the claim. With regard to claim 19, the MYOD1 gene analyzed by Chen II is "defined by the oligonucleotide primers and probes" of SEQ IDNOS 7-9. It is noted that this recitation has been broadly interpreted to encompass the gene which is can be analyzed by the recited SEQ ID NOS in the claim. The claims do not require analysis with the specifically recited SEQ ID NOS:.

Iacopetta teaches that regional hypermethylation of the Myf-3 (MYOD1) gene is an early and widespread event in colorectal neoplasia (see page 432, last para). The method of Iacopetta involves obtaining tissue from a test tissue to be diagnosed (see page 429, col. 2, 2nd full para; colorectal tissue), performing a methylation assay using restriction enzymes and nucleic acid probes (see page 429-430 bridging para; probe to 3' downstream region of Myf-3) to determine the methylation state of genomic CpG sequence for Myf-3. Iacopetta teaches that hypermethylation of the Myf-3 gene is strongly associated with the development of benign and malignant colorectal tumors, therefore Iacopetta teaches "making a diagnostic or prognostic prediction of the cancer based at least in part on the methylation state of the genomic CpG sequences (see page 431, col. 1, first sentence of "Discussion"). With regard to claim 18: the CpG sequences analyzed by Iacopetta 'correspond to CpG islands' which are 'associated' with

sequences defined by SEQ ID NOS 7-9. It is noted that this recitation has been broadly interpreted to encompass the gene which is can be analyzed by the recited SEQ ID NOS in the claim. With regard to claim 19, the MYOD1 gene analyzed by Iacopetta is "defined by the oligonucleotide primers and probes" of SEQ IDNOS 7-9. It is noted that this recitation has been broadly interpreted to encompass the gene which is can be analyzed by the recited SEQ ID NOS in the claim. The claims do not require analysis with the specifically recited SEQ ID NOS:.

Hahnel teaches a method which involves obtaining tissue from a test tissue to be diagnosed (see page 2111, col. 2, first full para; breast tissue), performing a methylation assay using restriction enzymes and nucleic acid probes (see page 2112 bridging para cols 1-2; probe to 3' downstream region of Myf-3) to determine the methylation state of genomic CpG sequence for Myf-3. Hahnel teaches that there was a statistically significant differenced in the hypermethylation in grade 3 carcinomas (see page 2112, 2nd col. Last para) and further teaches that hypermethylation of the Myf-3 gene was much more common in poorly differentiated (grade 3) breast carcinomas than in well differentiated tumors (grade 1 or 2) (see page 2114, col. 2), therefore Hahnel teaches "making a diagnostic or prognostic prediction of the cancer based at least in part on the methylation state of the genomic CpG sequences (see page 431, col. 1, first sentence of "Discussion"). With regard to claim 18: the CpG sequences analyzed by Hahnel 'correspond to CpG islands' which are 'associated' with sequences defined by SEQ ID NOS 7-9. It is noted that this recitation has been broadly interpreted to encompass the gene which is can be analyzed by the recited SEQ ID NOS in the claim. With regard to claim 19, the MYOD1 gene analyzed by Hahnel is "defined by the oligonucleotide primers and probes" of SEQ IDNOS 7-9. It is noted that this recitation has been broadly interpreted to encompass the gene which is can be

analyzed by the recited SEQ ID NOS in the claim. The claims do not require analysis with the specifically recited SEQ ID NOS:.

Neither Chen I nor Chen II nor Iacopetta nor Hahnel teach analysis of methylation alteration with DMH, however, Huang teaches the analysis of methylation status in nucleic acids using DMH, an array based analytical method that detects changes in methylation status based on arrays which comprise probes for screening methylation status of sequences (see abstract, page 468, col. 2). Huang teaches that the use of DMH allows for high density, DNA array based screening, and allows for more precise measurement of the frequencies and extent of methylation. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the analysis method used by Chen I or Chen II or Iacopetta or Hahnel, with the DMH analysis of Huang. The ordinary artisan would have been motivated to improve the methylation analysis of Chen I or Chen II or Iacopetta or Hahnel, because Huang teaches that analysis with DMH allowed for more precise measurement of the frequencies and extent of methylation. The ordinary artisan would have had a reasonable expectation of success that the DMH analysis method of Huang could be used instead of the analysis method used by Chen I or Chen II or Iacopetta or Hahnel because Huang teaches of successfully determining alterations in methylation patterns of nucleic acid in breast cancer analysis.

Conclusion

15. No claims are allowable.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jehanne Sitton

Jehanne Sitton
Primary Examiner
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11/10/04

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